Paper No. 70

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte PAUL R. SCHIMMEL

Appeal No. 2003-1335
Application No. 08/249,689[1]

HEARD: July 17, 2003

Before WILLIAM F. SMITH, SCHEINER and MILLS, Administrative Patent Judges.

SCHEINER, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the final rejection of claims 11-13, 17-19 and 21; claims 1, 3-10, 14-16 and 20, also pending in the application, have been allowed. The claims read as follows:

11. A complementary compound comprising hydrogen bond donor and acceptor sites arranged to specifically bind and inhibit the function of a targeted RNA molecule, wherein the compound is specifically directed to and binds to a critical region of the RNA molecule, located within the minor groove of the RNA molecule, identified by a combination of the primary, secondary and tertiary structure of the critical region.

12. The complementary compound of claim 11 wherein the RNA is selected from the group consisting of mRNA, tRNA, rRNA, and viral RNA.

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[1] Application for patent filed May 26, 1994. According to appellant, this application is a continuation of application serial no. 08/129,787, filed September 29, 1993, now abandoned, which is a continuation of application serial no. 07/586,534, filed September 21, 1990, now abandoned. This application is also related to application serial no. 07/929,834, filed August 14, 1992, now U.S. Patent 6,446,032.

13. The complementary compound of claim 11 further comprising a pharmaceutically acceptable carrier selected from the group consisting of pharmaceutically acceptable compositions for topical administration, pharmaceutically acceptable compositions for parenteral administration, pharmaceutically acceptable compositions for enteral administration, and combinations thereof.

17. The complementary compound of claim 12 wherein the compound binds to a critical region within the minor groove of the acceptor stem of a tRNA molecule.

18. The complementary compound of claim 17 wherein the tRNA molecule is $tRNA^{Ala}$.

19. The complementary compound of claim 17 wherein the critical region is the G3:U70 base pair.

21. The complementary compound of claim 11 wherein the compound is a nucleic acid and the compound is synthesized in vivo from a retroviral vector.

The issue appellant would have us consider is whether the specification provides an adequate written description of the subject matter of claims 11-13, 17-19 and 21. For the reasons which follow, we reverse the rejection with respect to claims 17-19, but affirm it with respect to claims 11-13 and 21.

PROCEDURAL HISTORY

This application has previously been on appeal (appeal no. 1997-2396). Following an oral hearing on February 6, 2001, we issued an opinion (dated April 30, 2001) reversing the examiner's rejection of claims 1 and 3-21 for lack of enablement under the first paragraph of 35 U.S.C. § 112, and entering a new ground of rejection against claims 11-13, 17-19 and 21 under the first paragraph of 35 U.S.C. § 112 for failure to provide an adequate written description of the claimed subject matter. As provided for under 37 CFR § 1.196(b)(1), appellant opted to amend the claims and continue prosecution of this matter before the examiner. The examiner maintained the new ground of rejection, and it is that rejection that is the subject of this appeal.

BACKGROUND

According to the specification, the invention "pertains generally to compounds and to the design of these compounds targeted to bind to ribonucleic acid [(RNA)]; and more particularly, to compounds that bind specifically to certain nucleotide base pairs in combination with elements of the secondary structure of the minor groove of [RNA] molecules." Page 1. Further according to the specification (pages 1 and 2):

> Three principal types of RNA exist in cells: messenger RNA, transfer RNA and ribosomal RNA. . . .
>
> The RNAs share a common overall structure, though each kind of RNA has a unique detailed substructure. Generally RNA is a linear, single-stranded . . . , repetitive polymer in which nucleotide subunits are covalently linked to each other in sequence. Each nucleotide subunit consists of a base linked to the ribose-phosphate of the polymeric backbone. The bases in RNA are adenine (A), uracil (U), guanine (G), and cytosine (C). The sequence of bases imparts specific function to each RNA molecule. Nucleotide bases from different parts of the same or different RNA molecules recognize and noncovalently bond with each other to form base pairs. Since RNAs generally are a single covalent strand, base pairing interactions are usually intrastranded . . . [and] play a major part in determining the three-dimensional structure of each of the RNAs and the interaction of RNA molecules with each other and with other molecules. . . .
>
> The RNA molecule forms a helix with major and minor grooves spiraling around the axis . . . Nucleotide bases are arranged near the center of the helix with the ribose phosphate backbone on the outside. The bases are planar, perpendicular to the axis, and stacked on one another. Because the helix is in the alpha form, bases and sequences of bases are most accessible from the minor groove, which is wider and more shallow than the major groove . . .

For a number of reasons discussed at length in the specification (e.g., pages 3, 4, 7, 8 and 17), "the primary basis for sequence discrimination in RNA is believed to be the minor groove." Specification, page 20.

DISCUSSION

Each of the claims on appeal is directed to a "complementary compound" capable of inhibiting the function of a targeted RNA molecule by binding a critical region within the minor groove of the targeted RNA molecule. "There are no examples of the design, synthesis of testing" of such compounds in the specification (Brief, page 10),[2] but the specification teaches that "the [complementary] compounds can be organic, inorganic, proteins, or even other nucleic acids" and "[s]pecific binding to the targeted molecule can be achieved by including in the [compound a] complementary nucleic acid sequence that forms base pairs with the targeted RNA under appropriate conditions, or by inclusion of chemical groups having the correct spatial location and charge" (specification, pages 38-39). "[I]n order for the compound to bind to the target RNA, hydrogen bond donor sites, hydrogen bond acceptor sites, and chemical side groups, have to be in the correct spatial location, orientation, and have the correct charge . . . this arrangement [ ] defines the structure of the compound" (Brief, page 7). As appellant explains, "[c]omplementary compounds are limited by the sequence of the RNA target molecule," thus, "only after obtaining the correct target RNA sequence, can the claimed compound and its structure be elucidated" (Brief, page 7). That is, "[t]he structural features common to the members of the claimed genus can only be determined once the hydrogen bonding arrangement of the target sequence is derived" (id.).

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[2] The Brief referred to throughout this opinion is Appellant's Substitute Appeal Brief, (paper no. 62, filed December 9, 2002).

The issue appellant would have us review is whether the specification provides an adequate written description for the subject matter of claims 11-13, 17-19 and 21 as required under the first paragraph of 35 U.S.C. § 112. In our view, the mutually dependent structural relationship between a target RNA and its complementary inhibitors is at the heart of this issue.

In Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) (citation omitted), the court stated that

> In claims to genetic material, [ ] a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function . . . does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. [ ] It is only a definition of a useful result rather than a definition of what achieves that result.

The court also stated that "[a] written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." Id. at 1567, 43 USPQ2d at 1405.

Recently, the court clarified this position, emphasizing that "[not] all functional descriptions of genetic material fail to meet the written description requirement," for example, "the written description requirement would be met for [a claim] . . . if the functional characteristic . . . were coupled with a disclosed correlation between that function and a structure that is sufficiently known or disclosed." See Enzo Biochem Inc. v. Gen-Probe Inc., 296 F.3d 1316, 1324-25, 63 USPQ2d 1609, 1613 (Fed. Cir. 2002).

The court adopted the PTO's internal guidelines for determining compliance with the written description requirement (Guidelines for Examination of Patent Applications Under the 35 U.S.C. § 112, ¶ 1, "Written Description Requirement, 66 Fed. Reg. 1099 (January 5, 2001), also available at http://www.uspto.gov/web/patents/guides.htm), at least to the extent that "the PTO would find compliance with § 112, ¶ 1, for a claim to an 'isolated antibody capable of binding to antigen X,' notwithstanding the functional definition of the antibody, in light of 'the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that antibody technology is well developed and mature.'" Enzo, 296 F.3d at 1324-25, 63 USPQ2d at 1613 (Fed. Cir. 2002).[3]

In the course of continuing prosecution of this application in the examining group, appellant amended claims 11-13, 17-19 and 21 to recite that the claimed compounds "compris[e] hydrogen bond donor and acceptor sites" "complementary" to a critical site in the minor groove the targeted RNA molecule. According to appellant, the claimed compounds "function to inhibit" a targeted RNA molecule, and the "hydrogen bond donor and acceptor sites [of the claimed compounds] are structural elements" "which define the landscape/topography of the claimed compound's surface" and which are "necessary to inhibit the function of a targeted RNA molecule" (Brief, pages 19 and

[3] The example referred to here stipulates that antigen X has been isolated and characterized and that the specification includes a complete protocol for its isolation. "Considering the routine art-recognized method of making antibodies to fully characterized antigens, the well defined structural characteristics for the five classes of antibody, the functional characteristics of antibody binding, and the fact that antibody technology is well developed and mature," the guidelines indicate that the written description requirement is met because "one of skill in the art would have recognized that the spectrum of antibodies which bind to antigen X were implicitly disclosed as a result of the isolation of antigen X" ("Application of Guidelines," Example 16, emphasis added).

20). Appellant argues that the "forces that provide for the exquisite complementarity at the interface between the antibody and its targeted epitope" (hydrogen bonding, van der Waals interactions, etc.) are the "exact forces [that] dictate[ ] the structure of the claimed compounds" (Brief, page 21). That being the case, appellant argues that the "claimed compounds [are described] in terms of both structure and function" (Brief, page 17), in a manner "parallel to . . . the 'isolation of antigen X' . . . example provided in the written description guidelines" (Brief, page 21), and therefore, the claims satisfy the written description requirement.

Having reviewed each of the claims in light of the standards discussed in Enzo, we have concluded that the specification provides an adequate written description for the subject matter of claims 17-19 because the structure of at least one of the two mutually dependent compounds, in this case, the RNA target molecule, is "sufficiently known or disclosed" (or as appellant puts it, "further defin[ed]" (Brief, page 4)). That is, in claim 17, the target RNA is identified as the acceptor stem of a tRNA molecule; in claim 18 the target RNA is the $tRNA^{Ala}$ molecule; and in claim 19, the target is identified as the G3:U70 base pair of the $tRNA^{Ala}$ molecule.[4] Thus, for the subject matter of these claims, a functional characteristic (binding and inhibition of target RNA) is coupled with "a structure that is sufficiently known or disclosed" (a transfer RNA). As appellant acknowledges, "the critical region of the targeted RNA molecule defines and limits the structure of the claimed genus of compounds" (Brief, page 8).

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[4] Appellant also argues that claim 12 "further defin[es] the targeted RNA" (Brief, page 4) of claim 11 as mRNA, tRNA, rRNA or viral RNA, but it is not clear how this further limits the targeted RNA as essentially all RNA fits into one of these categories.

Claims 11-13 and 21, however, stand on a different footing in that the target molecule, other than being identified as RNA, is completely undefined. That is, neither the identity of the inhibitory compound nor the identity of the target RNA is disclosed, thus the claimed compound is entirely abstract. Appellant argues that the hydrogen bond donor and acceptor sites are structural features tied to function, but merely stating that an unspecified compound has an arrangement of hydrogen bond donor and acceptor sites that allows the compound to bind a critical site in the minor groove of an unspecified RNA target molecule and inhibit RNA function does nothing to allow one skilled in the art to visualize or recognize the identity of the members of the genus. It may define a desirable result, but it does not define the inhibitor that achieves that result. That the "lock and key" mechanism of RNA inhibition may be analogous to the mechanism of antibody-antigen recognition is beside the point. Claims 11-13 and 21 do not parallel "the 'isolation of antigen X' . . . example provided in the written description guidelines" because there is no identification of an RNA target molecule in these claims. It is clear from Example 16 that "antigen X" represents a discrete antigen which serves as a reference point to define a genus of antibodies which are specific for antigen X. It is "the isolation of antigen X," coupled with "the level of skill and knowledge in the art of antibodies," that provides an adequate written description of "the spectrum of antibodies which would bind to antigen X" ("Application of Guidelines").

Appellant also argues that even though "[t]he structural features common to the members of the claimed genus can only be determined once the hydrogen bonding arrangement of the target sequence is derived," to do so would be "routine to those skilled in the art." That is, "[o]nce the RNA sequence is derived, the minor groove structure can be easily inserted into any number of commercially available computer

programs and the structural features of the [complementary] compound determined." Brief, page 7. In this regard, appellant has submitted a number of post-filing date "representative abstracts showing that compounds that bind within the minor groove to inhibit RNA function, as claimed, have been made" (Brief, page 10). While these arguments and references might be relevant in determining whether appellant's disclosure would have enabled one skilled in the art to make a complementary compound given a defined RNA target molecule, enablement is not the issue here, and the arguments and evidence have little to do with whether there is adequate written descriptive support for the claimed unspecified complementary compounds in the absence of a defined RNA target molecule. The severability of the enablement and written description requirements has long been recognized. See Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1561, 19 USPQ2d 1111, 1115. As explained in Vas-Cath,

> In a 1971 case [ ] involving chemical subject matter, the [Court of Customs and Patent Appeals] expressly stated that "it is possible for a specification to enable the practice of an invention as broadly as it is claimed, and still not describe that invention." In re DiLeone, 436 F.2d 1404, 1405, 168 USPQ 592, 593 (CCPA 1971) (emphasis added). As an example, the court posited the situation "where the specification discusses only compound A and contains no broadening language of any kind. This might very well enable one skilled in the art to make and use compounds B and C; yet the class consisting of A, B and C has not been described. Id. at 1405 n. 1, 168 USPQ 593 n. 1 (emphases in original).

Id. at 1561-62, 19 USPQ2d at 1115.

Appellant also offers two declarations (both submitted April 11, 2002) under the provisions of 37 CFR § 1.132: one by Dr. Julius Rebek, an expert in the field of molecular recognition; and one by Dr. James R. Williamson, an expert in the field of RNA and drug design in general. Both Dr. Rebek and Dr. Williamson provide more than ample evidence of the level of skill and understanding in the art at the time of the

invention. Dr. Williamson, for example, provides detailed evidence to support the assertion that it was known in the art, and disclosed in the specification, that "attractive and repulsive forces present in the critical region of the minor groove of RNA dictate or define the geometrical constraints of the region" and "[t]hese forces, as described in the specification . . . define the structure of the critical region in a way that provides one with a mental picture of a defined "space" that can only be accessed by a compound of the correct 'shape' . . . the minor groove [is] a 'lock' and the compound [is] the 'key'" (page 3). Given this level of skill and understanding, and the fact that "[t]hese features are easily obtained upon identifying the RNA sequence to be targeted' (page 7), Dr. Williamson concludes that "simply identifying the sequence of the nucleotides in the [minor] groove implies the specific conformation [of the RNA target], and defines the array of complementary groups [on the claimed inhibitor] that must be assembled in order to recognize that sequence" (page 9).

Both Dr. Williamson and Dr. Rebek, after evaluating the specification and claims, and the level of skill and understanding in the art, conclude that "the specification and claims, in view of what was known in to those in the art, provides a written description that is sufficient to comply with the legal standard" for written description (page 3 in each declaration), both experts having been advised (page 2 in each declaration) that "to comply with the written description [requirement], one must meet the following legal standard:

> . . . conception of a chemical compound requires that the inventor be able to define it so as to distinguish it from other materials, and to describe how to obtain it. Conception does not occur unless one has a mental picture of the structure of the chemical, or is able to define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it." [Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991)].

> Furthermore the court has stated that in order to satisfy the written description requirement, "the applicant need not describe the subject matter claimed in exact terms. However, the description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." [ ]

We have considered the facts and evidence presented by Drs. Rebek and Williamson, and agree that the evidence is compelling that one skilled in the art would be able to envision and/or make RNA inhibitors based on appellant's specification and the level of skill and understanding in the art, given a reasonably defined RNA target, the genus of transfer RNAs specified in claim 17, for example, but claims 11-13 and 21 do not define an RNA target except in the broadest possible terms. Inasmuch as the evidence establishes that the structure of the RNA target defines and limits the claimed complementary inhibitors, and the structure of the inhibitor can only be determined by elucidating the structure of the RNA target, and none of claims 11-13 and 21 specifies either of the mutually dependent compounds, we find that the evidence does not support a conclusion that one skilled in the art would be able to form a "mental picture of the structure of the chemical, or . . . define it by its method of preparation, its physical or chemical properties, or whatever characteristics sufficiently distinguish it." Amgen, 927 F.2d at 1206, 18 USPQ2d at 1021 (Fed. Cir. 1991).

Finally, appellant argues that the invention is a pioneering invention. We do not disagree, but it is well settled that such an invention is not "thereby entitled to a lower enablement requirement" than an invention not so designated. Plant Genetic Systems N.V. v. DeKalb Genetics Corp., 315 F.3d 1335, 1339, 65 USPQ2d 1452, 1455 (Fed. Cir. 2003). We know of no reason why the same would not be true of the requirement for an adequate written description.

CONCLUSION

We have affirmed the rejection of claims 11-13 and 21 as lacking an adequate written description under the first paragraph of 35 U.S.C. § 112, and reversed the rejection with respect to claims 17-19.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

William F. Smith
Administrative Patent Judge

Toni R. Scheiner
Administrative Patent Judge

Demetra J. Mills
Administrative Patent Judge

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